Claims

1 Process for the preparation of tetrahydropterin and tetrahydropterin derivatives by the hydrogenation of pterin and pterin derivatives with hydrogen in the presence of a hydrogenation catalyst, characterised in that the hydrogenation is carried out in a polar reaction medium and metal complexes that are soluble in the reaction medium are used as the hydrogenation catalysts.

2 Process according to claim 1, characterised in that the polar reaction medium is an aqueous or alcoholic reaction medium.

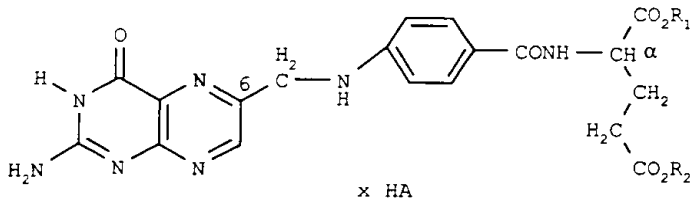
3 Process according to claim 1, characterised in that the pterin derivatives used are folic acid, folic acid salts, folic acid esters, folic acid ester salts or dihydroforms thereof for hydrogenation with hydrogen in the presence of a hydrogenation catalyst, the hydrogenation is carried out at elevated pressure in the presence of metal complexes dissolved in the reaction medium as hydrogenation catalysts, with the proviso that in the event of using folic acid, carboxylic acid salts thereof or dihydroforms thereof the reaction medium is aqueous, and in the event of using folic acid esters, folic acid ester salts or dihydroforms thereof the reaction medium is an alcohol.

4 Process according to claim 1 for the asymmetric hydrogenation of prochiral pterin derivatives with hydrogen in the presence of a hydrogenation catalyst, characterised in that the hydrogenation is carried out in a polar reaction medium and metal complexes that are soluble in the reaction medium are used as the hydrogenation catalysts, the metal complexes containing chiral ligands.

5 Process according to claim 4 for the asymmetric hydrogenation of folic acid, folic acid salts, folic acid esters, folic acid ester salts or dihydroforms thereof as pterin derivatives, with hydrogen in the presence of a hydrogenation catalyst, characterised in that the hydrogenation is carried out at elevated pressure in the presence of metal complexes dissolved in the reaction medium as hydrogenation catalysts, the metal complexes containing chiral ligands, with the proviso that where folic acid, carboxylic acid salts thereof or dihydroforms thereof are used, the

reaction medium is aqueous, and where folic acid esters, folic acid ester salts or dihydroforms thereof are used, the reaction medium is an alcohol.

6 Process according to Claim 5, characterised in that the folic acid ester salts satisfy formula III and are in the form of their enantiomers or mixtures,



x HA (III),

in which R_1 or R_2 is H, and R_2 or R_1, or both R_1 and R_2 independently of one another represent a monovalent hydrocarbon radical or a heterohydrocarbon radical attached via a carbon atom, with heteroatoms selected from the group comprising -O-, -S- and -N-,
HA stands for a monobasic to tribasic inorganic or organic acid,
and x denotes an integer from 1 to 6 or a fractional number between 0 and 6.

7 Process according to claim 6, characterised in that the acid HA in formula III is unsubstituted or substituted phenylsulphonic acid.

8 Process according to claim 1, characterised in that it is carried out at a hydrogen pressure of 1 to 500 bars.

9 Process according to claim 1, characterised in that the reaction temperature is 0 to 150°C.

10 Process according to claim 1, characterised in that the molar ratio of substrate to catalyst is 10 to 100 000.

11 Process according to claim 1, characterised in that the aqueous reaction medium is water or water in admixture with an organic solvent.

12 Process according to claim 1, characterised in that the alcoholic reaction medium is an alcohol, or an alcohol in admixture with an organic solvent.

13 Process according to claim 1, characterised in that the metal complexes contain a d-8 metal, preferably iridium, rhodium or ruthenium.

14 Process according to claim 1, characterised in that the metal complex contains achiral or chiral ditertiary diphosphines as ligand.

15 Process according to claim 14, characterised in that the ditertiary diphosphines for an alcoholic reaction medium are ones in which the phosphine groups are attached (a) to various carbon atoms of a hydrocarbon chain having 2 to 4 carbon atoms, or (b) directly or via a bridging group $-CR_aR_b-$ in the ortho positions of a cyclopentadienyl ring or to a respective cyclopentadienyl of a ferrocenyl, where R_a and R_b are the same or different and stand for H, C_1-C_8 alkyl, C_1-C_4 fluoroalkyl, C_5-C_6 cycloalkyl, phenyl, benzyl, or phenyl or benzyl substituted with 1 to 3 C_1-C_4 alkyl or C_1-C_4 alkoxy.

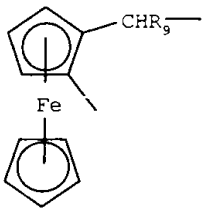
16 Process according to claim 15, characterised in that the diphosphines for an alcoholic reaction medium satisfy formula IV,

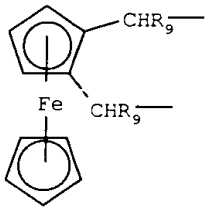
$$R_4R_5P\text{-}R_6\text{-}PR_7R_8 \qquad (IV),$$

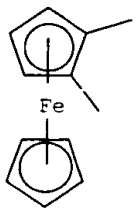
in which

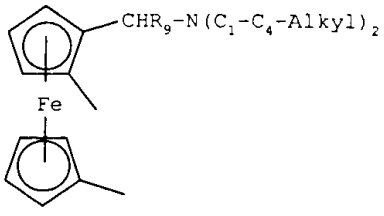
R_4, R_5, R_7 and R_8 independently of one another represent a hydrocarbon radical with 1 to 20 carbon atoms, which is unsubstituted or substituted with halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, $(C_6H_5)_3Si$, $(C_1$-C_12 alkyl$)_3Si$, $-NH_2$, $-NH(C_1$-C_{12} alkyl), -NH(phenyl), -NH(benzyl), $-N(C_1$-C_{12} alkyl$)_2$, -N(phenyl)$_2$, -N(benzyl)$_2$, morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, -ammonium-X_3^-, $-SO_3M_1$, $-CO_2M_1$, $-PO_3M_1$, or $-CO_2$-C_1-C_6 alkyl, in which M_1 represents an alkali metal or hydrogen, and X_3^- is the anion of a monobasic acid; or R_4 and R_5, and R_7 and R_8 respectively together denote tetramethylene, pentamethylene or 3-oxa-pentane-1,5-diyl, unsubstituted or substituted with halogen, C_1-C_6 alkyl or C_1-$_{C6}$ alkoxy; and

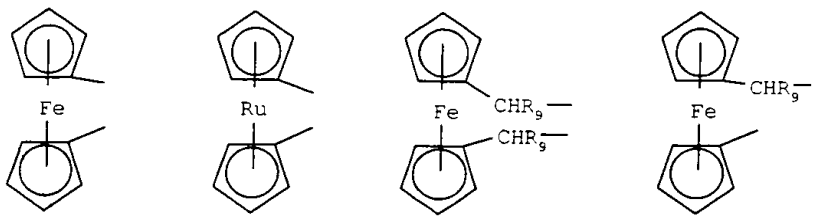
R_6 is C_2-C_4 alkylene, unsubstituted or substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, C_5 or C_6 cycloalkyl, phenyl, naphthyl or benzyl; 1,2- or 1,3-cycloalkylene, 1,2- or 1,3-cycloalkenylene, 1,2- or 1,3-bicycloalkylene or 1,2- or 1,3-bicycloalkenylene with 4 to 10 carbon atoms, unsubstituted or substituted with C_1-C_6 alkyl, phenyl or benzyl; 1,2- or 1,3-cycloalkylene, 1,2- or 1,3-cycloalkenylene, 1,2- or 1,3-bicycloalkylene or 1,2- or 1,3-bicycloalkenylene with 4 to 10 carbon atoms, unsubstituted or substituted with C_1-C_6 alkyl, phenyl or benzyl, at whose 1 and/or 2 positions or at whose 3-position methylene or C_2-C_4 alkylidene is attached; 1,4-butylene substituted in the 2,3 positions with $R_9R_{10}C(O-)_2$, and which in the 1 and/or 4 positions is unsubstituted or substituted with C_1-C_6 alkyl, phenyl or benzyl, and where R_9 and R_{10} independently of one another represent hydrogen, C_1-C_6 alkyl, phenyl or benzyl; 3,4- or 2,4-pyrrolidinylene or methylene-4-pyrrolidine-4-yl whose nitrogen atom is substituted with hydrogen, C_1-C_{12}- alkyl, phenyl, benzyl, C_1-C_{12} alkoxycarbonyl, C_1-C_8 acyl, C_1-C_{12} alkylaminocarbonyl; or denotes 1,2-phenylene, 2-benzylene, 1,2-xylylene, 1,8-naphthylene, 2,2'-dinaphthylene or 2,2'-diphenylene, unsubstituted or substituted with halogen, -OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, benzyl, phenyloxy or benzyloxy; or R_6 stands for a radical of the formulas







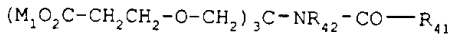




in which R_9 denotes hydrogen, C_1-C_8 alkyl, C_1-C_4 fluoroalkyl, unsubstituted phenyl or phenyl substituted with 1 to 3 F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 alkoxy or fluoromethyl.

17 Process according to claim 14, characterised in that diphosphines for an aqueous reaction medium are ones that contain one or more water-solubilising polar substituents, which are attached either direct or via a bridging group to substituents of the phosphine groups and/or to the skeleton of the diphosphine.

18 Process according to claim 17, characterised in that diphosphines for an aqueous reaction medium are ones of formula XLIII,



(XLIII)

in which M_1 stands for H, an alkali metal cation or an ammonium cation, R_{42} denotes C_1-C_4 alkyl and preferably H, and R_{41} is the monovalent radical of a chiral ditertiary diphosphine, with the CO group being attached direct to a carbon or nitrogen atom of the diphosphine skeleton, or to an oxygen or nitrogen atom or to a carbon atom of a bridging group of the diphosphine skeleton.

19 Process according to claim 1, characterised in that the hydrogenation catalysts are metal complexes of formulas XLIV, XLIVa and XLIVb,

$[X_7Me_2YZ]$ (XLIV), $[X_7Me_2Y]^+A_2^-$ (XLIVa), $[X_7Ru(II)X_8X_9]$ (XLIVb),

in which

Y for stands for two monoolefin ligands or a diene ligand;

X_7 represents an achiral or chiral ditertiary diphosphine that forms a 5 to 7 membered ring with the metal atom Me_2 or Ru;

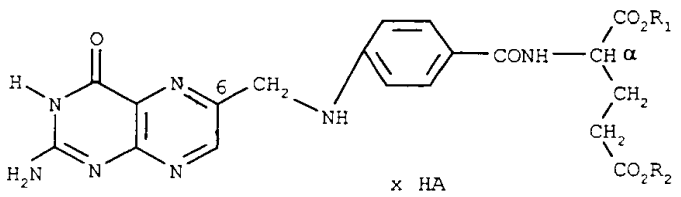
Me_2 denotes Ir(I) or Rh(I);

Z represents -Cl, -Br or -I; and

A_2 is the anion of an oxy-acid or complex acid,

X_8 and X_9 are the same or different and have the meaning of Z and A_2, or X_8 and X_9 stand for allyl or 2-methylallyl, or X_8 has the meaning of Z or A and X_9 stands for hydride.

20 Compounds of formula III in the form of their pure (αS) and (αR) enantiomers or mixtures thereof,



(III),

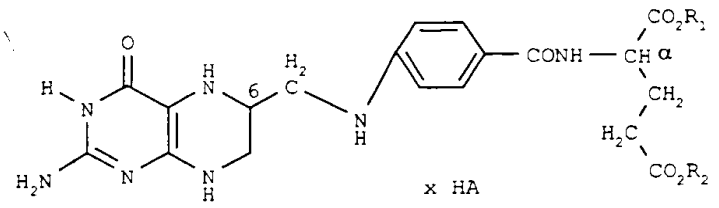
in which R_1 or R_2 are H, and one of R_1 or R_2, or both R_1 and R_2 independently of one another represent a monovalent hydrocarbon radical or a heterohydrocarbon radical attached via a carbon atom, with heteroatoms selected from the group comprising -O-, -S- and -N-,

HA stands for a monobasic to tribasic organic acid,

and x denotes an integer from 1 to 6 or a fractional number between 0 and 6.

21 Compounds according to claim 20, characterised in that R_1 and R_2 in formula III each denote methyl or ethyl, HA stands for benzene sulphonic acid or toluene sulphonic acid, and x is the number 1 or 2, or a fractional number between 0.5 and 2.

22 Compounds in the form of their pure diastereomers and mixtures thereof which satisfy formula IIIa,



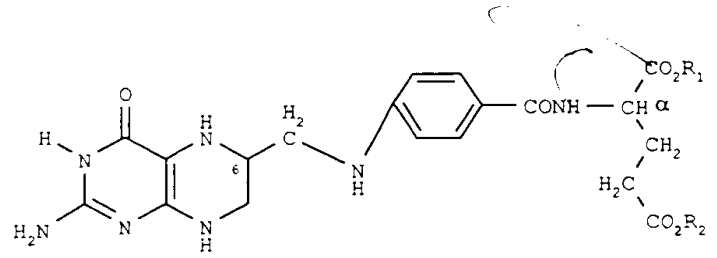
(IIIa),

in which R_1 or R_2 are H, and one of R_1 or R_2, or both R_1 and R_2 independently of one another represent a monovalent hydrocarbon radical or a heterohydrocarbon radical attached via a carbon atom, with heteroatoms selected from the group comprising -O-, -S- and -N-,
HA stands for a monobasic to tribasic inorganic or organic acid,
and x denotes an integer from 1 to 6 or a fractional number between 0 and 6.

23 Compounds according to claim 22, characterised in that R_1 and R_2 each represent C_1-C_{12} alkyl, HA stands for a monobasic to tribasic inorganic or organic acid, and x denotes an integer from 1 to 6 or a fractional number between 0 and 6.

24 Compounds according to claim 23, characterised in that R_1 and R_2 each represent methyl or ethyl, HA denotes benzene sulphonic acid or toluene sulphonic acid, and x stands for the number 1 or 2 or a fractional number between 0.5 and 2.

25 Compounds in the form of their pure diastereomers and mixtures thereof which satisfy formula IIIb,



(IIIb),

in which R_1 or R_2 are H, and one of R_1 or R_2, or both R_1 and R_2 independently of one another represent a monovalent hydrocarbon radical or a heterohydrocarbon

radical attached via a carbon atom, with heteroatoms selected from the group comprising -O-, -S- and -N-.

26 Compounds according to claim 25, characterised in that R_1 and R_2 in each case represent C_1-C_{12} alkyl.

27 Compounds according to claim 26, characterised in that R_1 and R_2 in each case represent C_1-C_4 alkyl.

28 Compounds according to claim 27, characterised in that R_1 and R_2 in each case represent methyl or ethyl.